REMARKS-General

The newly amended independent claim 36 incorporates all structural limitations of the originally amended independent claim 36 and includes further limitations previously brought forth in the disclosure. No new matter has been included. All claims 36-39 and 41-43 are submitted to be of sufficient clarity and detail to enable a person of average skill in the art to make and use the instant invention, so as to be pursuant to 35 USC 112.

With regard to the rejection of record based on prior art, Applicant will advance arguments to illustrate the manner in which the invention defined by the newly introduced claims is patentably distinguishable from the prior art of record. Reconsideration of the present application is requested.

Response to Rejection of Claims 36-39 under 35USC103

The Examiner rejected claims 36-39 as being unpatentable over Jones (US 5,741,491) in view of Yang et al (2003). Pursuant to 35 U.S.C. 103:

"(a) A patent may not be obtained thought the invention is **not identically** disclosed or described as set forth in **section 102 of this title**, if the **differences** between the subject matter sought to be patented and the prior art are such that the **subject matter as a whole would have been obvious** at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

In view of 35 U.S.C. 103(a), it is apparent that to be qualified as a prior art under 35USC103(a), the prior art must be cited under 35USC102(a)~(g) but the disclosure of the prior art and the invention are not identical and there are one or more differences between the subject matter sought to be patented and the prior art. In addition, such differences between the subject matter sought to be patented **as a whole** and the prior art are obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

In other words, the differences between the subject matter sought to be patent as a whole of the instant invention and Jones which is qualified as prior art of the instant

invention under 35USC102(b) are obvious in view of Yang et al. at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

The applicant respectfully submits that the differences between the instant invention and Jones are not obvious in view of Yang et al. under 35USC103(a), due to the following reasons:

(A) Regarding the newly amended independent claim 36, the examiner is of the view that it would have been obvious to one having ordinary skill in the art to combine the teaching of Jones with the Toona sinensis extract disclosed in Yang et al, in order to produce the instant invention. The applicant respectfully submits that Jones and Yang fails to anticipate a herbal composition comprising a predetermined quantity of Toona sinensis for exerting an effect of lowering blood glucose level and a predetermined quantity of Heracleum lanatum for posing anti-inflammatory effect on said patient, wherein when the composition is ***prepared*** by the steps recited in (a) to (e), and that the composition is ***administered*** through the steps recited in the newly amended independent claim 36, the result for treating diabetes is ***unexpectedly good***.

(B) In order to support the unexpectedly good treatment result of the instant invention, the applicant respectfully submits a ***Clinical Trial Report*** which details the results and reduction of glucose level of patients (For summary of result, see Page 58 of the report).

(C) The applicant respectfully submits that to reject claims in a patent application under 35 U.S.C. 103, the Examiner must show an unrebutted prima facie case of obviousness. See *In re Deuel*, 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

A prima facia case of obviousness requires setting forth:

(a) the differences in the claim over the applied references,

(b) the proposed modification of the applied references necessary to arrive at the claimed subject matter, and

(c) an explanation why such proposed modification would be obvious. MPEP §706.02. In establishing a prima facie case of obviousness, the Examiner must make the four factual inquiries sent forth by the Supreme Court in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the four factual inquiries required by Graham are as follows:

(a) Determining of the scope and contents of the prior art;

(b) Ascertaining the differences between the prior art and the claims in issue;

(c) Resolving the level of ordinary skill in the pertinent art; and

(d) Evaluating evidence of secondary consideration.

These factors have not been appropriately applied in this case. In addition, when applying 35 USC 103, the following tenets of patent law must be adhered to:

(a) The claimed invention must be considered as a whole;

(b) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(c) The references must be viewed without the benefit of hindsight vision afforded by the claimed invention; and

(d) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug. Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

As established below, these factors and criteria clearly point to the nonobviousness of the claimed invention. In particular, Jones and Yang et al. fail to anticipate that the composition as recited in the newly amended claim 36 could have produced the effective result of treating diabetes.

(D) Regarding claim 37, Jones and Yang et al. fail to anticipate that the Toona sinensis is leaves of Toona sinensis and the Heracleum is roots of Heracleum lanatum, in addition to what is claimed in the newly amended independent claim 36 as a whole.

(E) Regarding claims 38-39, Jones and Yang et al. fail to anticipate that said quantity of Toona sinensis is not less than said quantity of Heracleum lanatum by weight, in addition to what is claimed in the newly amended independent claim 36 as a whole.

The Cited but Non-Applied References

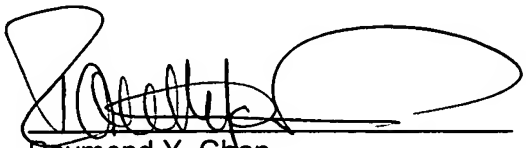
The cited but not relied upon references have been studied and are greatly appreciated, but are deemed to be less relevant than the relied upon references.

A fee in an amount of US$405.00 is submitted herewith to pay the fee for Request for Continued Examination (RCE). This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 502111.

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of the rejection are requested. Allowance of claims 36-39 at an early date is solicited.

Should the examiner believes that anything further is needed in order to place the application in condition for allowance, he is requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Raymond Y. Chan
Reg. Nr.: 37,484
108 N. Ynez Ave.
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Monterey Park, CA 91754
Tel.: 1-626-571-9812
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CERTIFICATE OF MAILING

I hereby certify that this corresponding is being deposited with the United States Postal Service by First Class Mail, with sufficient postage, in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" on the date below.

Date: 12/12/2007

Signature: 

Person Signing: Judith Wong

CLINICAL TRIAL REPORT

For

PROTOCOL ID: VL/051171/SVG

A non-comparator, multi centric, pilot study to investigate the safety, tolerability and anti-hyperglycaemic effects of a combination of Toona sinensis and Heracleum lanatum when given as an add-on therapy with Oral Hypoglycaemic Agent to patients with Type 2/ Non-Insulin Dependent Diabetes Mellitus.

Version 1.0 Dated 01.06.07

CERTIFICATE OF COMPLIANCE

This is to certify that this study has been successfully conducted in compliance with ICH-GCP, Protocol, SOP's & Guidelines, applicable Regulatory requirements & Contractual agreements and that the final report has been written in compliance with ICH-E3 guidelines.

K V Mehta

Komal Mehta

Project Manager

Jayesh Chaudhary

Jayesh Chaudhary

CEO

VEDIC LIFESCIENCES PVT. LTD.
natural products research & regulatory affairs

Email: vedic@ayuherbal.com, Website: www.vediclifesciences.com

TITLE PAGE

Study Title	A non-comparator, multi centric, pilot study to investigate the safety, tolerability and anti-hyperglycaemic effects of "a combination of Toona sinensis and Heracleum lanatum" when given as an add-on therapy with Oral Hypoglycaemic Agent to patients with Type 2/ Non-Insulin Dependent Diabetes Mellitus
Investigational Product	Combination of Toona sinensis & Heracleum lanatum.
Indication Studied	Type 2 / Non-Insulin Dependent Diabetes Mellitus
Name and Address of Sponsor	Mr. Leonard Lee Body Right Inc. 31855 Date Palm Dr. Suite 3, Unit 153 Cathedral City, Ca. 92234 USA
Protocol Identification No.	VL/051171/SVG
Development Phase of Study	PHASE IIa (Exploratory Study)
Study Initiation Date (Date of first patient enrolled)	September 29, 2006
Study Completion Date (Date of last patient completed)	April 26, 2007
Name of Sponsor Signatory	S. V. Ganesh Inc. 323, Cain Court, Belle Mead, NJ-08502, USA. Tel: 630-540-9936, 877-707-2853 E-mail: ajayc@patmedia.net
Name and Address of the CRO	Vedic Lifesciences Pvt. Ltd. 118, Morya House, Off New Link Road, Andheri (West) Mumbai: 400 053, India Tel: 91-22-26733092/93 Fax: 91-22-66941179 E-mail: vedic@ayuherbal.com clinical@ayuherbal.com
Central Laboratory	Metropolis Health Services (India) Ltd. 250 D, Udyog Bhavan, Behind Glaxo, Hind Cycle Marg, Worli, Mumbai- 400 030, India Tel: 91-22-66505599
Statement of GCP-Compliance	The above-mentioned study was carried out in compliance with ICH-GCP guidelines and Indian GCP guidelines[1, 2]. Study documents are archived with Vedic Lifesciences Pvt. Ltd., Mumbai, INDIA.

SIGNATURE PAGE

Protocol ID: VL/051171/SVG

Title: A non-comparator, multi centric, pilot study to investigate the safety, tolerability and anti-hyperglycaemic effects of "a combination of Toona sinensis and Heracleum lanatum" when given as an add-on therapy with Oral Hypoglycaemic Agent to patients with Type 2/ Non-Insulin Dependent Diabetes Mellitus.

I have read this report and confirm to the best of my knowledge it accurately describes the conduct and results of the study

Name : Jayesh Chaudhary

Position : Chief Executive Officer

Address : Vedic Lifesciences Pvt. Ltd.
118, Morya House,
Off. New Link road,
Andheri-(West)
Mumbai-400 053, India

Date : October 11, 2007

Signature : 

LIST OF TABLES, CHARTS AND GRAPHS

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
CRO	Contract Research Organisation
DBP	Diastolic Blood Pressure
DCF	Data Clarification Form
DF	Degree of Freedom
FBS / FPG	Fasting Blood Sugar / Fasting Plasma Glucose
GCP	Good Clinical Practices
HbA1c	Glycosylated Hemoglobin
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention to Treat
N	Number of Subjects
NR	Not Related
NS	Non-Significant
PP	Per Protocol
PPBS	Post-Prandial Blood Sugar
PR	Pulse Rate
QOL	Quality of Life Questionnaire
R	Related
RR	Respiratory Rate
S	Significant
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
T	Temperature

REPORT SYNOPSIS

Title Of Study	A non-comparator, multi centric, pilot study to investigate the safety, tolerability and anti-hyperglycaemic effects of "a combination of Toona sinensis & Heracleum lanatum" when given as an add-on therapy with Oral Hypoglycaemic Agent to patients with Type 2/ Non-Insulin Dependent Diabetes Mellitus.		
Sponsor	Mr. Leonard Lee Body Right Inc. 31855 Date Palm Dr. Suite 3, Unit 153 Cathedral City, Ca. 92234 USA		
Designated contact Person from Sponsor	S. V. Ganesh Inc. 323, Cain Court, Belle Mead, NJ-08502, USA. Tel: 630-540-9936, 877-707-2853 E-mail: ajayc@patmedia.net		
Test Product	Pancresinens Tablets		
Active Ingredients	Toona sinensis (Chinese Toona) Heracleum lanatum (Cow Parsnip)		
Investigators & Study Centers	Site 1: Dr. Vyankatesh Shivane Ashoka Polyclinic, Shreeram Chawl, P. B. Road, Near Century Quarters, Worli, Mumbai-400013, INDIA Site 2: Dr. Mahendra Patel Patel's Diabetes Care Centre, Laxmi Niwas, Vartak Nagar, Thane-400606, INDIA		
Date of First Subject Enrolled	September 29, 2006	**Date of Last Subject Completed**	April 26, 2007
Phase of Development	PHASE IIa (Exploratory Study)		
Objectives	Primary: To evaluate the efficacy of "a combination of Toona sinensis & Heracleum lanatum" when given as add on therapy to Oral Hypoglycaemic agents (OHA) in patients with Type 2 / Non-Insulin Dependent Diabetes Mellitus.		

<table>
<tr><td></td><td colspan="3">Secondary: To evaluate the safety and tolerability of "a combination of Toona sinensis & Heracleum lanatum" when given as add on therapy to Oral Hypoglycaemic agents (OHA) in patients with Type 2 / Non-Insulin Dependent Diabetes Mellitus.</td></tr>
<tr><td>Methodology</td><td colspan="3">Subjects (n= 39) with Type 2/Non-Insulin Dependent Diabetes Mellitus having HbA1c 8-10 % and Fasting Blood Sugar less than or equal to 200 mg/dl with stable daily dose of Sulfonylurea or Metformin or Combination of both were enrolled into the study. After enrolment, Investigational Product was given and subjects were followed up every 15 days. Subject's clinical examination and monitoring of adverse/serious adverse events was done at all visits (Day 1, Day 15, Day 30, Day 45, Day 60, Day 75 and Day 90 whereas laboratory based safety assays were done at Day 0 and at end of the treatment (Day 90). Primary efficacy variable (HbA1c) was assessed at Day 1, Day 45 and Day 90 whereas Fasting & Post-Prandial Blood Sugar, Quality of Life was assessed at all visits for all subjects. At the end of therapy, tolerability of IP, patient's opinion about continuing treatment & investigator's comments about efficacy of IP was assessed.</td></tr>
<tr><td rowspan="2">Number of Recruited Subjects</td><td>Completed cases Planned</td><td>Recruited</td><td colspan="2">Analyzed</td></tr>
<tr><td rowspan="2">30</td><td rowspan="2">39</td><td>Per ITT</td><td>Per Protocol</td></tr>
<tr><td>38</td><td>28</td></tr>
<tr><td>Diagnosis & Main Criteria of Inclusion</td><td colspan="3">Male and female patients with a history of Type 2/Non-Insulin Dependent Diabetes Mellitus for not more than five years and of age between 20-60 years receiving stable daily dosage of Oral Hypoglycaemic Agent (Sulfonylurea or Metformin or combination of Sulfonylurea & Metformin) for at least two months having Glycosylated Haemoglobin 8-10 % & Fasting Blood Sugar less than or equal to 200 mg/dl were enrolled in the study after taking written informed consent from all screened patients.</td></tr>
</table>

Treatment	Dose	Mode Of Administration	Batch Number
Test Product (Combination of Toona sinensis & Heracleum lanatum.)	2 Tablets thrice daily before meals. (Pre Breakfast, Pre Lunch, Pre Dinner)	Oral	BR1223
Duration Of Treatment		90 Days	
Criteria for evaluation			
Safety Parameters	• Vital parameters; (Pulse Rate, Temperature, Respiratory Rate & Blood Pressure) • Laboratory Tests (CBC, ESR, SGPT,S. Creatinine, Urine Routine & Microscopy and ECG) • Incidence & nature of adverse and/or serious adverse events		
Efficacy Parameters	• HbA1c • Fasting and Post-Prandial Blood Sugar • Quality of Life (Polyurea, Polyphagia, Pain & Leg Cramps)		
Statistical Methods	Software Used: SPSS 11.5, PEPI, EPI INFO 2000 and MS Excel Tests Applied: ANOVA Test, Paired t-test, Chi-square test, Friedman test, Wilcoxan test. Sets of Analyses: Intention To Treat analyses (LOCF procedure), Per protocol analyses.		
Safety Results	Vital parameters and laboratory safety parameters remained unchanged throughout and at the end of the treatment. IP was found to be well tolerated by study population. There were 12 AE s reported out which 10 were not related to IP and 2 were possibly related to IP. There was one serious adverse event reported which was not related to IP.		

Efficacy Results	28 subjects out of the 39 completed the study as per the protocol. 28 subjects when analyzed by per protocol mode showed significant ($p < 0.05$) reduction in HbA1c, FBS and PPBS at Day 45, Day 60 and Day 60 respectively. There was a reduction seen even at Day 90 but not statistically significant. When effcacy assessed by investigator, it was found that 15.80 %, 23.70, 31.60 and 28.90 % of study patients showed excellent (Improvement in all parameters), good Improvement in more than 2 parameters), average (Improvement in less than 2 parameters) and poor (No improvement) efficacy respectively. 71.10 % of the study patients showed willingness to continue the study treatment for Type 2 Diabetes Mellitus.
Conclusion	The a combination of Toona sinensis and Heracleum lanatum when given as an add on therapy along with oral hypoglycemic agent (OHA) to patients with Type 2 Diabetes Mellitus was found to be clinically effective ($p < 0.05$ at Day 45 and Day 60; $p > 0.05$ at Day 90) in providing better glycemic control and it was found to have an excellent safety and tolerability profile under the conditions of the study.

1. INTRODUCTION

Type 2 diabetes is the most common form of diabetes, accounting for 90% to 95% of all cases. It usually develops in adults of age 40 years and older and is most common in adults over 55 years (NIH, 2004). Type 2 diabetes is usually part of a cluster of other metabolic abnormalities, including obesity and elevated blood pressure and lipids. Major risk factors for type 2 diabetes include old age, obesity, family history of diabetes, race/ethnicity. Complications related to diabetes include diabetic nephropathy, neuropathy, retinopathy, cardiovascular risk and skin conditions[3, 4].

Oral treatment includes sulfonylureas, biguanides (metformin) and thiazolidinediones. Patients not adequately controlled on combined oral therapy may require insulin.

The modern management of diabetes in spite of many advances still remains unsatisfactory due to drug intolerance, hypersensitivity, resistance to insulin, the danger of acute and chronic complications, the fear of hypoglycaemic episodes and weight gain with sulfonylurea.

Given this situation the trial was designed to explore the anti diabetic effects and possible side effects of "a combination of Toona sinensis and Heracleum lanatum". Positive findings in the most ideal situation could include "a combination of Toona sinensis & Heracleum lanatum to have a significant glycaemic control compared to baseline with a favourable safety profile, when given as an add on therapy with OHA, which could be further explored in new clinical trials with larger populations against conventional therapy.

For this trial, being an exploratory study, a small sample size was agreed of 30 subjects to complete the study till the End of Treatment visit (Day 90). Keeping a minimum rate of 20% of withdrawals and drop outs in mind, this implicated that we had to include at least 36 patients.

Guidelines that were followed in developing the protocol included the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

The sponsor had a written agreement with the CRO and with the Clinical Trial Supply Manufacturer. The CRO made further written agreements with Investigators and companies for Clinical Trial Insurance and Laboratory Assessments.

The purpose of the present clinical study was to investigate the efficacy, safety and tolerability of "a combination of Toona sinensis and Heracleum lanatum."

2. ETHICS

2.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The written approval of study documents inclusive protocol amendments was received from an Independent Ethics Committee "IRB of K. J. Somaiya Medical College and Hospital, Mumbai". The list of IEC members of IEC are given in Appendix 11.1.5 and IEC approval letters are given in Appendix 11.1.6.

2.2 Ethical Conduct of the study

The study was conducted in compliance with the protocol and SOPs, the ethical principles that have their origin in the ICH-GCP and after receiving written approval from above mentioned IEC.

2.3 Patient Information and Consent

The Patient Informed Consent Form was provided to all the study sites in English as well as three local languages (Hindi, Marathi & Gujarati). After receiving written informed consent, the subjects were enrolled in the study.

The sample Patient Consent Form is given in Appendix 11.1.4.

3 STUDY ADMINISTRATIVE STRUCTURE

Contract Research Organization (CRO)		Vedic Lifesciences Pvt. Ltd. (VL) 118 Morya House, Off. Link Road, Andheri (West), Mumbai-400053, INDIA.
Project Manager		Komal Mehta, B. Pharm.
Monitors		Amol Shindikar; B. Pharm.
Site	**Investigator**	
1	Dr. Vyankatesh Shivane, M.B.B.S; D.Diabetology; Ph.D. (Endo.)	
2	Dr. Mahendra Patel, M.B.B.S; D.Diabetology	
Data Management		
Data Manager		Dr. Navneet Sonawane, BAMS
Bio-Statistician		Dr. Harshad Thakur, MD
Medical Writer		Dr. Navneet Sonawane, BAMS
Clinical Trial Insurance Company		National Insurance Co. Ltd. 3 Middleton Street , Kolkata 700 071, INDIA.

The Curriculum Vitae of all the members mentioned above is been given in Appendix 11.1.7.

4 STUDY OBJECTIVES

Primary objectives:

- To evaluate whether "a combination of Toona sinensis and Heracleum lanatum" is effective in patients with Type 2/No-Insulin Dependent Diabetes Mellitus.

Secondary objective:

- To evaluate the safety and tolerability of "a combination of Toona sinensis and Heracleum lanatum" in patients with Type 2/Non-Insulin Dependent Diabetes Mellitus.

Evaluation Criteria:

Primary Criteria:
- HbA1c
- Fasting & Post-Prandial Blood Sugar
- Quality of Life

Secondary Criteria:
- Vitals (Pulse Rate, Respiratory Rate, Blood Pressure & Temperature)
- Laboratory Tests (CBC, ESR, SGPT, Creatinine, Urine Routine & Microscopy and ECG)
- Nature, Incidence and Severity of Adverse & /or Serious Adverse Events
-Tolerability

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan Description

Study Configuration	An exploratory, non-comparator, multi-centric study
Patient population studied	Male & female patients with not more than 5 years history of Type 2/Non-Insulin Dependent Diabetes Mellitus with glycemic control (HbA1c) of 8-10 % and FBS less than or equal to 200mg/dl.
Number of patients recruited in study	39
Treatments Studied	Combination of Toona sinensis & Heracleum lanatum.
Method of treatment assignment	Patients satisfying all the selection criteria were screened. Informed Consent from the patients was taken before they were enrolled in the study. Since this was a non-comparator study wherein IP was given as an add on therapy to OHA, eligible patients were assigned to treatment in the serial number of the enrolment.

Study Design and Schedule of Assessments

Chart 1: Study Flow Chart

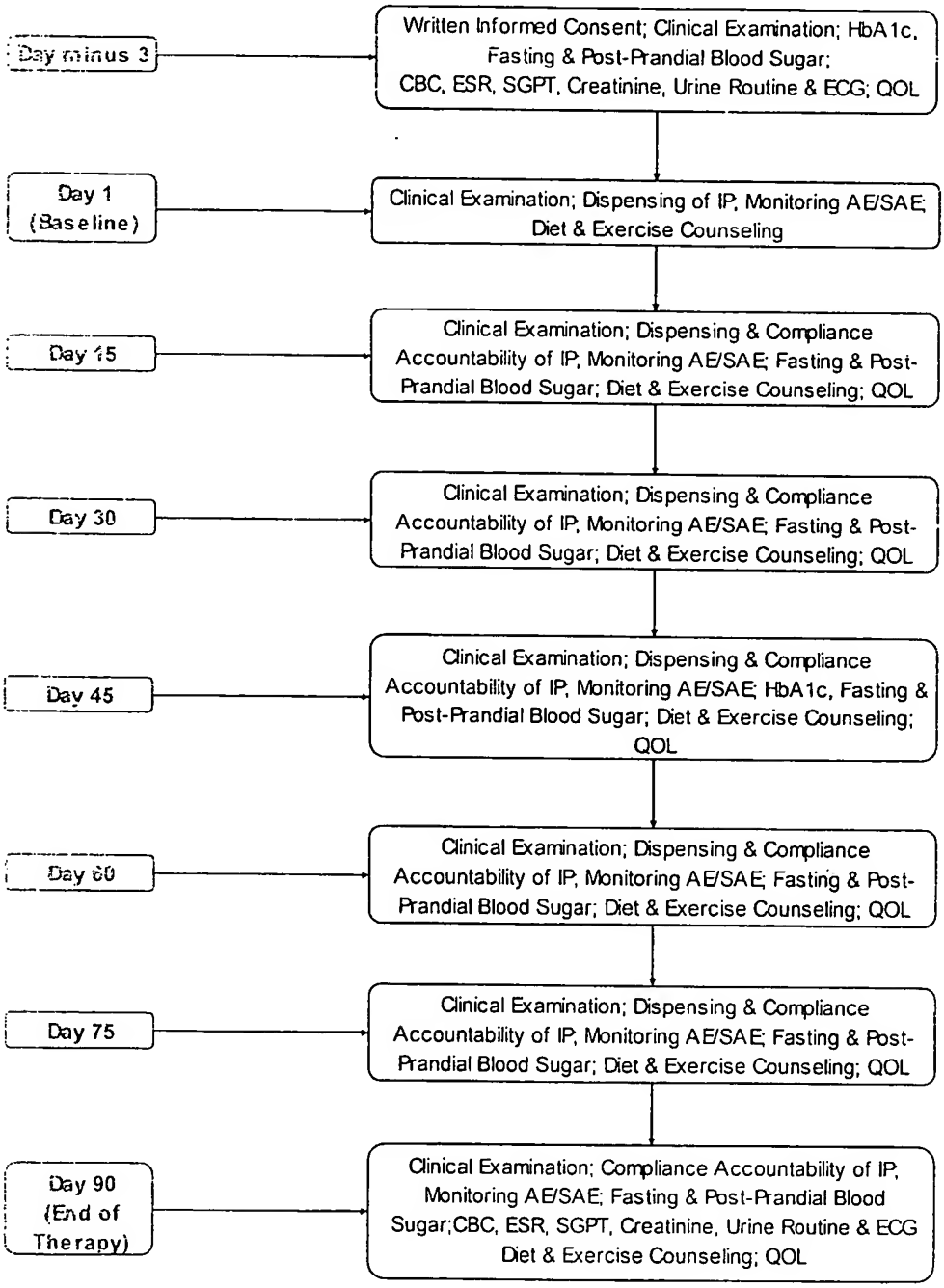

Chart 2: Schedule of Assessments

Parameters	D –3	D –2	D 1	D 13	D 15	D 28	D 30	D 43	D 45	D 58	D 60	D 73	D 75	D 88	D 90
Vitals	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
Systemic Examination	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X
History of disease	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CBC	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
ESR	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
SGPT	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
Serum Creatinine	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
Urine Routine	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
ECG	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
HbA1c	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-
Fasting Blood Sugar	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-
Post-Prandial Blood Sugar	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-
Body Weight	X	-	-	-	-	-	X	-	-	-	X	-	-	-	X
Body Mass Index	X	-	-	-	-	-	-	-	-	-	X	-	-	-	X
Diet and exercise Counselling	-	-	X	-	X	-	X	-	-	-	X	-	X	-	X
Dispensing of IP	-	-	X	-	X	-	X	-	X	-	X	-	X	-	-
IP Compliance	-	-	-	-	X	-	X	-	X	-	X	-	X	-	X
Monitoring AE/SAE	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X
QOL- Questionnaire	-	-	X	-	X	-	X	-	X	-	X	-	X	-	X

NOTE: "X" indicates the parameters evaluated.

Visits on Day -2, Day 13, Day 28, Day 43, Day 58, Day 73 and Day 88 were kept in the visit specific schedule so that patients can get the lab investigations done on these visits and investigators can check their reports on their follow up visits with patients on Day 1, Day 15, Day 30, Day 45, Day 60, Day 75 and Day 90 visits respectively after receiving the reports from laboratory.

5.2 Discussion of Study Design

This was a multi-centric study for evaluation of safety, tolerability and efficacy of a combination of Toona sinensis and Heracleum lanatum. Subjects were selected such that they had not more than 5 years history of Type 2/Non-Insulin Dependent Diabetes Mellitus with HbA1c of 8-10 % with stable daily dosage of Sulfonylurea or Metformin or combination of both. This was done so as to assess if a combination of Toona sinensis and Heracleum lanatum can provide better glycemic control when given as an add on therapy along with OHA. Patients with less than 5 years history of diabetes were taken so as to avoid diabetic complications which may worsen during the course of the study. Patients with Fasting Blood Sugar more than 200 mg/dl were not included as in these cases immediate medical care would have been necessary which would have led to high withdrawal rate due to hyperglycaemia. Dose of OHA was kept unchanged through out the study so that effect of a combination of Toona sinensis and Heracleum lanatum can be assessed at the end of therapy as compared to baseline. In order to assess anti-hyperglycaemic effects of "a combination of Toona sinensis & Heracleum lanatum", HbA1c, FBS, PPBS, Quality of Life, subject's opinion and investigator's assessment about efficacy were measured whereas to assess the safety, vital parameters, examination of various systems of body, laboratory based assays and monitoring adverse/severe adverse events were measured.

5.3 Selection of Study Population

5.3.1 Inclusion Criteria

- Male and Female Patients with history of Type 2 /Non-Insulin Dependent Diabetes Mellitus for not more than five years.
- Patient with age between 20 and 60 years.
- Patients with Body Mass Index between 20 and 35 kg/m^2
- Patients taking any stable daily dosage of oral hypoglycaemic agent-Sulphonylurea or Metformin of Combination of Sulphonlyurea and Metformin (not more than 75 % of recommended maximal dose) for at least two months.
- Patients with stable HbA1c between 8-10 % and Fasting Plasma Glucose less than or equal to 200 mg/dl.
- Patients willing to give written informed consent and come for regular follow up.

5.3.2 Exclusion Criteria

- Patients with type 2 diabetes who are difficult to control with respect to glucose homeostasis (non-stable patients), which will be decided by Investigator on clinical history of patients.
- Patients who are secondary oral hypoglycaemic agent failures.
- Patients who, in addition to the oral anti hyperglycaemic drug also require insulin
- Patients who can be controlled by a changed life style (e.g. exercise, reduced body weight)
- Pregnant and nursing women
- Diabetic complications requiring treatment
- Clinically significant abnormality in any of the laboratory safety parameters.
- Serious hepatic or renal impairment
- Significant cardiovascular co-morbidities, e.g. symptomatic heart failure, a history of ischemic heart disease, history of stroke and/or Transient Ischemic Attack as evident from ECG.
- Debilitating neurological or psychiatric disorders
- Known hypersensitivity or allergy to one or more of the herbal ingredients used in Investigational Product.
- Recent (< 3 months) participation in a clinical trial
- Recent (< 3 months) use of any herbal/ayurvedic anti-diabetic drugs
- Any condition likely to hinder the compliance with the protocol.

5.3.3 Removal of Subjects from Therapy/Assessment

The following criteria were used for removal of subjects from therapy.

Withdrawal Criteria

- Earnest request of the patient assigning a reason for the same.
- Discretion of the investigator.
- Repeated protocol criteria deviations
- Adverse or serious adverse events where continuation of study possess serious risk to the patient.
- If FPG is less than or equal to 60 mg/dl or If FPG > or equal to 216 then the subject should be withdrawn from the study.
- Patient has consumed less than or equal to 80% of the total dose that needs to be consumed in the period between follow-ups.
- Patient consumes any other anti-diabetic agent (allopathic / herbal)
- Patient is without medication for more than 7 days consecutively.
- Patient is without medication for 4 to 6 consecutive days and in the opinion of the investigator needs to be withdrawn from the study. (Investigator Discretion needed)

Protocol Deviation

Following will be deemed as protocol deviations:

- Patient takes any other medicines for any other complaints without consulting investigator.
- Patient does not bring left over study medication at the time of follow up visit.
- Patient does not get laboratory testing within +3 or -3 days of scheduled visit.

5.4 Treatments

5.4.1 Treatments Administered

Investigational Product	
For Therapy	Combination of Toona sinensis and Heracleum lanatum
Route of administration	Oral
Dosage	2 Tablets thrice daily before meals. (Pre Breakfast, Pre Lunch and Pre Dinner)
Batch Number	BR1223
Manufacturer	Santos Nutraceutical Corp.

5.4.2 Identity of Investigational Product (s)

The formula is as mentioned below.

Table 1: **Common names and composition of Investigational Product**

NAMES	COMMON NAMES	COMPOSITION
Toona sinensis (Meliaceae)	Chinese Toona	700 mg
Heracleum lanatum (Umbelliferae)	Cow Parsnip	300 mg
Excipients	-	q.s.

Toona sinensis is originated from China. It is a grey, rough dark colour in the bark of trunk and distribution all over the world now. The whole plant including seeds, epidermal layer of root, bark, stem and leaves has been used for health supplement or for treatment of disease. It is highly recognised by the Chinese Practitioners that the leaves extract of Toona sinensis is capable of effectively lowering the blood glucose level of diabetics, even for those diabetics who have extraordinary high blood glucose level and are not responsive to the conventional medications. Furthermore, it is effective in improving the body conditions against development of long-term or related complications, such as body pain, unstable blood pressure and numbing of four limbs. T.

sinensis has also been used for treating pimples, common cold, waist pain and arthritis caused by uric acid. For the treatment of diabetes, the whole plant of Toona sinensis may be used but the leaf portion is preferred.

Research in analysing the effect of T. sinensis on treatment for diabetes showed that leaves of Toona sinensis are capable of lowering the blood glucose level of Alloxan induced diabetes in mice without lowering the blood glucose level of normal mice in control group. It stimulates the secretion of insulin and promotes the performance of the lipid tissue of glucose transferase. In fact, both old aged leaves and new shoot are effective in treating diabetes.

T. sinesis has also been used for enhancing health conditions because of its high nutritional value. Preliminary studies on T. sinesis showed that it could lower blood pressure and some documentation stated that it has haemostatic effect. Furthermore, T. sinensis is capable of reliving pain in oral medication form, anti-inflammatory in highly concentrated form, promoting coagulation in different concentration of T. sinensis, anti-oxidant effect in low dose extract, increasing life time expectancy and increasing the strength of respiratory system in septicaemic mice, improving the function of liver and increasing the activity level of sperm.

Heracleum lanatum is a sturdy herbaceous perennial which is native to North America and is found from Labrador to Alaska, south to the mountains of Georgia and west to California. Native Americans used the cooked roots for intestinal disorders, the seeds in headache remedies, raw pieces of the root to alleviate toothaches when used as stuffing in dental cavities and many other remedies.

In Alaska, the insides of the raw stems and roots are used for sugar extraction. In Arizona, young leaves and stems are used for cooking and roots are used for treating epilepsy. The root is believed to be beneficial in relieving gas and cramps.

It is known that H. lanatum is a remedy for the stomach and nervous system. The root is usually made into a tea for nausea. The seed tincture is a good analgesic for sore tooth with less irritating effect to the gums. The roots or seed is antispasmodic to the intestinal tract. However since H. lanatum contains sterols and saponins, it is not advised to use during pregnancy.

Since diabetes is also a state of inflammation, a lowering of seriousness of inflammation may greatly promote a body condition which in turn provide a maximum body condition to response positively to any treatment of diabetes. H. lanatum having an anti-inflammatory effect is ideal for providing a maximum body condition for treating diabetes.

A combination of use of T. sinensis and H. lanatum has been studied and is found that a herbal composition comprising of T. sinensis and H. lanatum is capable of having positive effect on the treatment of diabetes, arthritis and neuralgia and is effective in lowering blood pressure. H. lanatum posing anti-inflammatory effect on a body helps to release the tension caused by inflammation, while at the same time the T. sinensis exerts its effect of lowering blood glucose level. Thus, the combination of use of the T. sinensis and H. lanatum is interactively providing an elevated effect for treatment of diabetes.

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The composition of T. sinensis and H. lanatum is effective in treating diabetes and inflammation. T. sinensis is the active ingredient for treating diabetes while the H. lanatum is the active ingredient for providing an optimum environment and conditions for the T. sinensis. H. lanatum is effective in treating inflammation; it can reduce the severity of inflammatory level of digestive tract including pancreas such that a more anti-inflammatory status of the digestive tract is achieved. On the other hand T. sinensis is capable of having a better environment and thus has its optimum effect in stimulating secretion of insulin and hence lowering glucose level.

Test Specifications

Description	Greyish green coloured elongated biconvex uncoated tablet with yellow mottling on it
Carbohydrates	0.22 gm/tab
Protein	0.16 gm/tab
Total fat	0.03 gm/tab
Saturated fat	Nil
Calories	3.86 calories/tab
Sodium	17.8 mg/tab
Calcium	247.1 mg/tab
Potassium	17.4 mg/tab
Iron	3.074 mg/tab
Vitamin A & C	Identified

5.4.3 Selection of Doses in the Study

Acute Oral Toxicity Study of a combination of Toona sinensis and Heracleum lanatum was carried out in Sprague Dawley Rats in which sighting study revealed mild loco motor activity with onset at 1hour after the dosing. The signs were observed for first six hours after the dosing at the dose level of 2000 mg/kg. All animals survived the study period. Therefore the main study was continued at the dose level of 2000 mg/kg body weight.

The main study revealed mild reduced loco motor activity with onset at 1 hour after the dosing. The signs were observed for first six hours after the dosing at the dose level of 2000 mg/kg. All animals survived the study period. Gross pathological examination did not reveal any abnormalities.

It was concluded that the acute toxicity study of a combination of Toona sinensis and Heracleum lanatum when administered via oral route in Sprague Dawley rats falls into the category 5 criteria of Globally Harmonized System (GHS).

5.4.4 Prior and Concomitant Therapy

None of the enrolled subjects were allowed to undergo any special change in dietary habits, medication, lifestyle, or exercise schedule after their enrolment in the study, which may influence sugar level. During the course of the study, the subjects were not allowed to consume i) any other anti-diabetic preparation; ii) any other herbal medicine during the course of the trial.

Subjects were not allowed to change the dose of OHA during the therapy.

Subjects who were required to take medicines for any other complaint (s) or concomitant disease (s) during the course of the study were allowed to take medicines only after consultation with the investigator and record of the same was maintained in the Case Report Form.

In case of withdrawals or after completion of study, subjects were allowed to switch over to earlier allopathic medication and /or any other treatment as recommended by the Investigator.

5.4.5 Treatment Compliance

Investigational Product was given in the form of tablets, one bottle (108 tablets in each bottle) at each visit every 15 days. At each visit, IP was given with 3 days extra supply so as to make sure that none of the subjects were off the medications in case of deviation from schedule for follow up visit. Investigator was instructed to counsel the subjects properly about the use of the IP. The account of returned and dispensed IP was maintained in the IP accountability record in Site Master File at site and in monitoring file. Subjects were withdrawn from the study if they were without IP for more than 7 days consecutively or if compliance of IP was less than or equal to 80% of the total dose that was needed to be consumed in the period between follow-ups.

Chart 3: IP Accountability Record

Patient ID	Day 1		Day 15			Day 30			Day 45			Day 60			Day 75			Day 90	
	Dt	Di	Dt	Di	Re	Dt	Di	Re	Dt	Di	Re	Dt	Di	Re	Dt	Di	Re	Dt	Re

Di: Number of tablets dispensed.
Re: Number of tablets returned
Dt:Date

5.5 Efficacy and Safety Variables

5.5.1 Efficacy and Safety Measurements Assessed

A) Specifications of Safety Variables

Vitals:

- Pulse Rate (Per minute)
- Temperature (Degree Celsius)
- Respiratory Rate (Per minute)
- Blood Pressure (mm of Hg)

Systemic Examination:

- Gastrointestinal System (heartburn, belly pain, diarrhoea, nausea)
- Respiratory System (Shortness of breath, Wheezing, Coughing)
- Central Nervous System (Numbness, Weakness, Headache)
- Cardiovascular System (Chest pain, Irregular Heartbeat)
- Genitourinary System (pain, frequent urination, blood in urine)
- Head & Neck
- Extremities
- Skin

Laboratory Assessments:

- Complete Blood Count (CBC)
- Erythrocyte Sedimentation Rate (ESR)
- Serum Glutamate Pyruvate Transaminase (SGPT)
- Serum Creatinine
- Urine Routine & Microscopy

Adverse and/or Serious Adverse Events:

Any adverse effect observed, or suspected causal relationship to the IP was recorded on the adverse event page of the case record form. Events involving the adverse drug reaction, illnesses with onset, during the study or exacerbation of pre – existing illnesses were recorded. Follow – up of the adverse event, even after the date of discontinuation of the therapy was required if the adverse effect or its sequel persisted. Follow up was required until the event or its sequel resolved or stabilized at a level acceptable to the investigator. For capturing adverse and /or serious adverse events, an AE/SAE form was provided as a part of CRF at each visit for investigators to enter the details of the event. The Case Report Form containing the Adverse Drug Event Form is provided in Appendix 11.1.3.

Tolerability:

This parameter was used to assess the overall tolerability of the IP. The gradation of which was done as mentioned below. Appropriate option was tick marked by the investigator.

☐ Good – No side effects

☐ Fair – Mild to moderate side effects

☐ Poor – Severe side effects requiring withdrawal of therapy

B) Specifications of Efficacy Variables

HbA1c was used as the Primary Efficacy Variable. Haemoglobin is the component in the red blood corpuscles (RBC's) that transports oxygen. Haemoglobin occurs in several variants; the one which composes about 90% of the total, is known as Haemoglobin A. A1c is a specific subtype of Haemoglobin A. The 1 is actually a subscript to the A, and the c is a subscript to the 1. Glucose binds slowly to Haemoglobin A, forming the A1c subtype. Since the normal life span of RBC's is 90-120 days, the A1C will only be eliminated when the red cells corpuscles are replaced; A1C values are directly proportional to the concentration of glucose in the blood over the full life span of the RBC's. A1C values are not subject to the fluctuations that are seen with daily blood glucose monitoring. The A1C value is an index of mean blood glucose over the past 2-3 months but is weighted to the most recent glucose values. Values show the past 30 days as ~50% of the A1C, the preceding 60 days giving ~25% of the value and the preceding 90 days giving ~25% of the value. This bias is due to the body's natural destruction and replacement of RBC's [11]. The American Diabetes Association (ADA) recommends A1C as the best test to find out if a subject's blood sugar is under control over time.

-HbA1c is about 6 per cent of the total Haemoglobin in people who don't have diabetes. This is the target to aim for with tight blood sugar control - although 7 % or less is very good.

-HbA1c of 7.5 % shows only fair control of diabetes.

-HbA1c above 8.5 % shows poor control of diabetes.

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) studies showed that the lower the A1C number, the greater the chances to slow or prevent the development of serious eye, kidney and nerve disease. It showed that for every 1 per cent rise in HbA1c, a person with Type 2 diabetes is 30 per cent more likely to develop late-stage complications arising from damage to the small blood vessels. The studies also showed that any improvement in A1C levels can potentially reduce complications. The ADA recommends that action be taken when A1C results are over 8%, and considers the diabetes to be under control when the A1C result is 7% or less. Based on the possible fluctuation with Plasma Glucose levels and also on the basis of profile of HbA1c, it was used as the Primary Efficacy Variable with frequency of three readings over a period of 90 days therapy.

Since HbA1c is the representative of glucose control over 2-3 months, Blood Sugar Level was used as secondary efficacy variable. Normally, blood glucose levels stay within narrow limits throughout the day: 4 to 8mmol/l. But they are higher after meals and usually lowest in the morning.

In diabetes the blood sugar level moves outside these limits until treated. Even with good control of diabetes, the blood sugar level will still at times drift outside this normal range.

When very high levels of blood glucose are present for years, it leads to damage of the small blood vessels. This in turn increases risk of developing late-stage diabetes complications such as: retinopathy (eye disease), nephropathy (kidney disease), neuropathy (nerve disease), cardiovascular disease, such as heart attack, hypertension, heart failure, stroke and problems caused by poor circulation, e.g. gangrene in the worst cases.

- **Quality of life Questionnaire**: At every visit the subject's health and tolerance was monitored through a Questionnaire [10].

SYMPTOM	GRADE	DESCRIPTION
POLYURIA	0	1-4 frequency in day time 0-2 frequency in night and normal volume
	1	5-7 frequency in day time 3-5 in night time with excessive volume
	2	8-10 frequency in day time and 6-8 frequency in night time with excessive volume
	3	Increased frequency of urination and thirst (once in 2 hours) and intake is in excessive amount.
POLYPHAGIA	0	Two main meals + 1 light breakfast (normal quantity).
	1	Two main meals and 2-3 light snacks (normal quantity).
	2	Two main meals, and 2-3 light snacks with increased quantity
	3	Two main meals and 3-5 light snacks with increased quantity.
	4	Two main meals and more than 5 snacks with increased quantity
PAIN (Either in the body, joints or limbs)	0	No pain in routine activity
	1	Pain, which does not disturb routine activity.
	2	Pain with slight limitations of movements disturbing the routine activity.
	3	Pain with severe limitation of movements and activity reduced remarkably.
LEG CRAMPS	0	No leg cramps
	1	Mild leg cramps
	2	Moderate
	3	Severe
WEAKNESS	0	Routine activity without feeling of weakness
	1	Patient feels weakness during routine activity
	2	Routine activity of the patient disturbed but the patient is not bed ridden.
	3	Patient is hospitalized/bed ridden

- **Subject's Opinion:**

At the end of trial, a question was asked to each subject by the investigator on the subject's opinion of the IP. The appropriate option was tick marked.

Would you like to continue the same treatment for diabetes?

Yes ----------/ No ----------

- **Assessment of Efficacy by Investigator:**

Based on various parameters, the overall assessment about the efficacy of IP was done for each subject by the investigator. The appropriate option was tick marked.

- ☐ **1**- Excellent: Improvement in all parameters
- ☐ **2**- Good: Improvement in more than 2 parameters
- ☐ **3**- Average: Improvement in less than 2 parameters
- ☐ **4**- Poor: No improvement

The timing of study visits and the procedures to be carried out at each visit are shown in Chart 2.

Chart 4: Timings of Measurement of Safety and Efficacy Variables

Parameters	D -3	D1	D 15	D 30	D 45	D 60	D 75	D 90
Safety Variables								
Vitals	X	X	X	X	X	X	X	X
Systemic Examination	X	X	X	X	X	X	X	X
CBC & ESR	-	X	-	-	X	-	-	X
SGPT	-	X	-	-	X	-	-	X
Serum Creatinine	-	X	-	-	X	-	-	X
Urine Routine	-	X	-	-	X	-	-	X
ECG	-	X	-	-	X	-	-	X
Monitoring of AE/SAE	-	X	X	X	X	X	X	X
Tolerability	-	-	-	-	-	-	-	-
Efficacy Variables								
HBA1c	-	X	-	-	X	-	-	X
Fasting Blood Sugar	-	X	X	X	X	X	X	X
Post-Prandial Blood Sugar	-	X	X	X	X	X	X	X
Body Weight	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X
Quality of Life	X	X	X	X	X	X	X	X
Subject's Opinion	-	-	-	-	-	-	-	X
Assessment of efficacy by investigator	-	-	-	-	-	-	-	X

5.5.2 Appropriateness of Measurements

This study involved HbA1c and blood sugar levels as the efficacy variables. In order to minimize lab to lab variation in the test results, NABL & CAP certified central laboratory "Metropolis Health Services (India) Ltd." was selected. This assured the quality of safety and efficacy test results. For other subjective parameters like vitals, systemic examination, quality of life, investigators opinion about the overall efficacy, tolerability etc., investigators were trained at the time of site initiation for accurate and adequate collection of data. During monitoring also these aspects were checked by monitors to assure credibility of the data.

5.6 Data Quality Assurance

In order to assure the quality of trial, various measures were taken.

For both the sites, Site Initiation Visit was made in presence of Investigator,. and Study Coordinators to train them about ICH-GCP and important trial related aspects like adherence to protocol, screening and recruitment of eligible subjects only after written informed consent, CRF filling and updating of source documents, Handling of IP etc. The Site initiation Reports are provided in Appendix 11.1.9

Regular Monitoring Visits were made to sites in order to assure the performance of site as per the protocol and GCP. During each monitoring visit, Site Master File for various records like Screening Log, Enrolment Log, IP Accountability Record was checked; CRF's were verified using source documents; IP accountability was checked for all the subjects manually to assure adequate handling as per the protocol. The monitors reviewed case record forms for completeness and accuracy, and instructed site personnel to make any required corrections or additions. The Monitoring Reports are provided in Appendix 11.1.10

After the study completion, all the sites were closed. At the site close out visit, CRF's and all the documents in Site Master File were checked for accuracy and completion. Study related documents and IP were retrieved from all the sites and archived in office of Vedic Lifesciences Pvt. Ltd. (VLS)

The Data Management was done in house at Vedic Lifesciences .The Data Manager & Data Entry operators were appointed for the same, following the in house guidelines for Data Management Procedures.

The Study Database was designed using Microsoft Access .The data entry screens were designed as close as possible to the CRF structure to enable data entry personnel to enter data without any major queries. After the designing of Data entry screens, dummy data entry was done for a few subjects. Testing of Validation Procedures was also done for the database. Guidelines were followed for data entry, double data entry and validation. The discrepancies were resolved by raising Data Clarification Forms (DCF). The DCF's were resolved with concerned investigators of respective sites. Once all DCF's were closed, the authorized person locked the database. A database lock log was maintained for reference.

5.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

5.7.1 Determination of Sample Size

Since this was an exploratory, pilot study there was no statistical method used for sample size determination. 30 subjects were planned to complete Day 90 visits, End of Treatment. For this target 39 subjects were ultimately recruited in the trial, resulting in 28 subjects who completed Day 90 visits, End of Treatment.

5.7.2 Statistical Evaluation Plan

The principal hypotheses to be investigated are:

- A combination of Toona sinensis and Heracleum lanatum is effective in providing better glycaemic control compared to baseline.
- A combination of Toona sinensis and Heracleum lanatum is safe and tolerable in subjects with Type 2/Non-Insulin Dependent Diabetes Mellitus

The statistical evaluation plan was decided as follows:

1. The analysis was planned at 95% confidence levels.
2. Two sets of Analysis were planned
    - Per Protocol Analysis was done for completed cases; i.e. the subjects who completed the study till Day 90.
    - The Intention to Treat Analysis was done for all the subjects who followed up at least for one visit after receiving IP.
3. Assessment of Vitals and Systemic Examination included both qualitative & quantitative variables. The quantitative variables like Pulse, Respiratory rate, Temperature were planned to be analysed by using quantitative statistical tests like paired t test and ANOVA for comparing data of the visits to that of Day 1 visit.
4. Quality Of Life – Questionnaire mainly contains ordinal variables & it was planned to be analysed by using non parametric tests like Friedman test, Wilcoxan Matched Pairs Signed Ranks test.
5. The following Statistical Softwares were planned to be used: - SPSS 11.5, PEPI, EPI INFO 2000 and MS Excel XP.

5.8 Changes in the Conduct of the Study or Planned Analysis

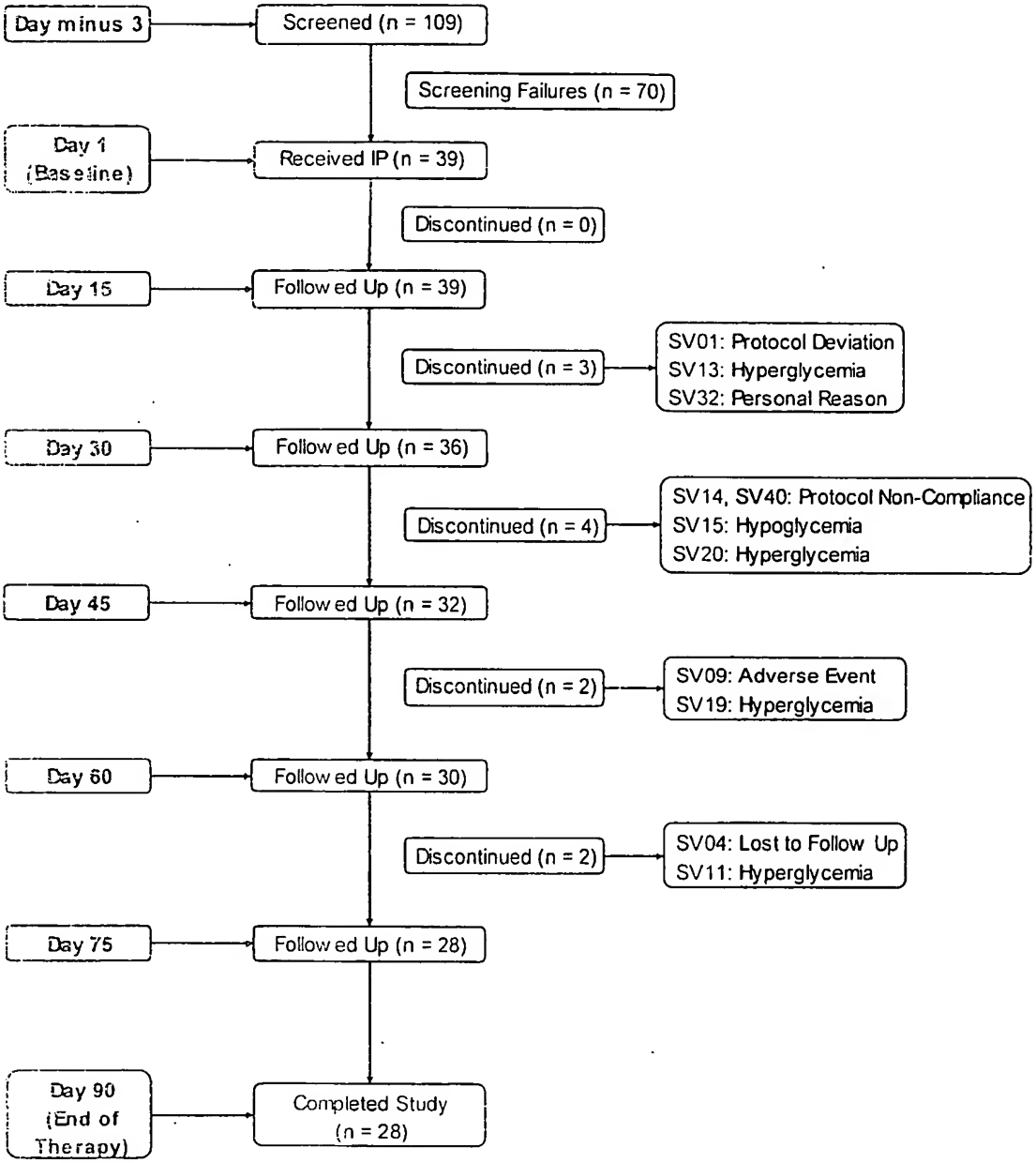
The study objectives, efficacy and safety parameters and statistical plan were laid down in the protocol before commencement of the study.

There were no changes made in the conduct of the study or the statistical plan for the study.

6 STUDY SUBJECTS

6.1 Disposition of Subjects

Chart 5: Disposition of Patients, Withdrawals and Drop outs



5.2 Protocol Deviations

There were no major protocol deviations found during the conduct of study.

7 SAFETY EVALUATION

7.1 Extent of Exposure

The extent of exposure to Investigational Product according to the number of subjects exposed and the duration of exposure to which they were exposed is as mentioned below.

Table 2: Extent of Exposure to IP

Patient ID	No. of Patients	Extent of exposure (Days)
SV01, SV13, SV32	3	15
SV14, SV15, SV20, SV40	4	30
SV09, SV19	2	45
SV04, SV11	2	60
SV02, SV03, SV05, SV06, SV07, SV08, SV10, SV12, SV16, SV17, SV18, SV21, SV22, SV23, SV26, SV27, SV28, SV29, SV30, SV31, SV33, SV34, SV35, SV36, SV37, SV38, SV39, SV41	28	90

7.2 Adverse Events

7.2.1 Brief Summary of Adverse Events

Table: 3: Brief Summary of Adverse Events

AE/SAE	Mild		Moderate		Severe		Total		Total
	R	NR	R	NR	R	NR	R	NR	R + NR
Rhinitis	-	SV01[4]	-	SV16[4]	-	-	-	2	2
Tinea Vulgaris	-	SV04[4]	-	-	-	-	-	1	1
Giddiness	-	SV05[4]	-	-	-	-	-	1	1
Heart Burn	SV09[2]	-	-	-	-	-	1	-	1
Pain in Legs	-	SV16[5]	-	-	-	-	-	-	1
Backache	-	SV20[5]	-	-	-	-	-	1	1
Dry Cough	SV23[4]	-	-	-	-	-	1	-	1
Itching over dorsum of left foot	-	-	-	SV27[4]	-	-	-	1	1
Burning of sole	-	SV30[4]	-	-	-	-	-	1	1
Vomiting	-	SV37[4]	-	-	-	-	-	1	1
Reddish Papule on Forehead & Forearm	-	SV05[4]	-	-	-	-	1	-	1
Weakness	-	SV18[5]	-	-	-	-	-	1	1

Relation of AE with IP:
1: Definite
2: Possible
3: Probable
4: Not Related
5: Unknown

7.2.2 Deaths and Other Serious Adverse Events

1. No deaths occurred during the study.
2. One Serious Adverse Event was reported during the study, the details of which are as mentioned below.

Centre Code: VLSVG02

Patient ID: SV08

Age: 59 Years

Sex: Female

Date of IP started: 06.10.2006

Description of Event:

The subject had a history of bilateral immature cataract since screening visit. Ophthalmologist had advised right eye cataract surgery.

Action Taken:

The subject was admitted 0n 23.11.2006 and discharged on 25.11.2006. Right eye cataract surgery with posterior chamber intraocular lens implantation was done under local anaesthesia on 24.11.2006.

Relation of SAE with IP: Not Related

7.3 Vital Signs, Laboratory Findings and Other Observations Related to Safety

For assessment of safety of IP, Intention to Treat Analysis has been done for vital parameters, laboratory findings and tolerability.

7.3.1 Vital Parameters

The mean values of the vital parameters like Pulse Rate, Respiratory Rate and Temperature are provided in tables.

Table 4: Changes in Vital Parameters as Compared to Baseline

Vitals	Mean ± Std. Dev. (N)						
	Day 1	Day 15	Day 30	Day 45	Day 60	Day 75	Day 90
PR (Per minute)	80.78 ± 4.32 (38)	81.05 ± 4.82[b] (38)	81.30 ± 4.01[b] (36)	81.75 ± 4.56[b] (32)	81.56 ± 5.61[b] (30)	80.57 ± 5.18[b] (28)	80.06 ± 6.29[b] (29)
RR (Per minute)	17.15 ± 1.36 (38)	17.07 ± 1.19[b] (38)	17.05 ± 1.21[b] (36)	17.33 ± 1.19[b] (33)	17.29 ± 1.32[b] (31)	17.24 ± 1.64[b] (29)	19.26 ± 11.63[b] (30)
SBP (mm of Hg)	121.42 ± 12.40 (38)	122.05 ± 8.58[b] (38)	122.44 ± 10.58[b] (36)	123.63 ± 14.03[b] (33)	122.00 ± 11.33[b] (31)	120.62 ± 10.67[b] (29)	120.41 ± 12.06[b] (29)
DBP (mm of Hg)	77.21 ± 6.31 (38)	78.57 ± 5.48[b] (38)	77.66 ± 4.31[b] (36)	78.12 ± 6.03[b] (33)	76.86 ± 6.07[b] (31)	77.00 ± 4.57[b] (29)	76.82 ± 5.16[b] (30)
Using Paired t test : a=significant ($p < 0.05$) as compared to baseline b= not significant ($p > 0.05$) as compared to baseline							

7.3.2 Laboratory Parameters

Table 5: Changes in Laboratory Parameters as Compared to Baseline

Laboratory Safety Parameters	Mean ± Std. Dev.	
	Day 1 (N = 38)	Day 90 (N = 30)
Hb (gm/dL)	13.67 ± 1.69	13.41 ± 1.94[b]
Neutrophils (%)	54.76 ± 8.19	55.50 ± 10.63[b]
Basophils (%)	0.00	0.00
Eosinophils (%)	4.86 ± 3.37	4.60 ± 2.85[b]
Lymphocytes (%)	34.18 ± 8.40	34.13 ± 10.35[b]
Monocytes (%)	6.18 ± 1.48	5.86 ± 1.47[b]
Total WBC (per c.mm.	7087.63 ± 1899.82	7427.66 ± 1700.68[b]
Total RBC (milli/c.mm.)	4.91 ± 0.49	4.78 ± 0.53a
ESR (mm)	11.56 ± 9.24	12.83 ± 11.90[b]
SGPT (U/L)	26.31 ± 16.83	24.06 ± 13.24[b]
S. Creatinine (mg/dL)	0.90 ± 0.22	0.86 ± 0.24[b]
Using Paired t test : a=significant ($p < 0.05$) as compared to baseline b= not significant ($p > 0.05$) as compared to baseline		

7.4 Assessment of Tolerability

Table 6: Assessment of Tolerability

Tolerability	
Grade	**N (%)**
Very Good: No side effects	37 (97.40 %)
Good: Mild side effects	01 (2.60 %)
Fair: moderate side effects	-
Poor: Severe side effects requiring withdrawal of therapy	-
Total	**38 (100 %)**

7.5 Safety Results

All vital parameters (Pulse Rate, Respiratory Rate and Blood Pressure (Table: 4) remained unchanged ($p > 0.05$) throughout the trial. No clinically significant findings were reported in any of the vital parameters.

All the laboratory safety parameters remained unchanged ($p > 0.05$) throughout the trial except for Total RBC count, where there was a statistically significant reduction ($p < 0.05$) at the end of treatment (Table: 5).

IP was found to be well tolerated. 97.40 % of the total study population showed no side effects indicating very good tolerability (Table: 6).

Total 12 AEs were reported. 2 patients reported rhinitis. Other AEs included, Tinea Vulgaris, Giddiness, Heart Burn, Pain in Legs, Backache, Dry Cough, Itching over dorsum of left foot, Burning of sole, Vomiting, Reddish papule on forehead & forearm and Weakness. Out of the 12, 10 were of mild severity and only 2 AEs were of moderate severity. Only 1 AE i.e. Heart Burn was found to be possibly related to IP as assessed by the investigator (Table: 3).

No deaths were reported during the trial. One serious adverse event was reported however it was not reported to have any relation with IP.

8 EFFICACY EVALUATION

8.1 Data Sets Analyzed

Both efficacy and safety analyses were based on the actual treatment received. Two types of analyses were done as mentioned below. However, SV01 was considered for any of the analyses as it was a case of protocol deviation.

A. Per Protocol Analysis/Completed subjects: For this analysis, those subjects (N = 28) who completed the study till Day 90 were considered as completed cases.

B. Intention To Treat Analysis: All subjects (N = 38) who received IP and had at least one follow up after receiving therapy on Day 1, whether or not completed study visit Day 90, were considered for this analysis. Last Observation Carried Forward (LOCF) method was used to replace missing data.

8.2 Demographics and Other Baseline Characteristics

Table 7: Demographics and Other Baseline Characteristics

DEMOGRAPHICS								
Study Centre	SV01				SV02			
N (%)	8 (21.05 %)				30 (78.95 %)			
Age (Mean ± Std.	49.18 ± 7.35							
Body Mass Index	24.91 ± 3.46							
Gender	Male				Female			
N (%)	21 (55.30 %)				17 (44.70 %)			
Diet	Vegetarian				Occasionally Non-Vegetarian			
N (%)	6 (15.80 %)				32 (84.20 %)			
Current OHA Therapy	Glibenclamide				Glimeperide		Metformin	
N (%)	3 (7.90 %)				20 (52.60 %)		15 (39.50 %)	
History of Concomitant Disease (s)	Hyperlipidemia	Hypertension	Bilateral Mature Cataract	Bilateral Knee Joint Pain	Peripheral Neuropathy	Weakness	Body ache	Pain in Legs
N (%)	9 (23.08%)	6 (15.38%)	1 (2.56%)	1 (2.56%)	2 (5.13%)	1 (2.56%)	1 (2.56%)	1 (2.56%)

8.3 Efficacy Results and Tabulations of Individual Subject Data

8.3.1 Analysis of Efficacy

For parameters like HbA1c, FBS, PPBS and Quality of Life, Per Protocol as well as Intention to Treat Analyses were done.

For parameters like subject's opinion about continuing treatment and assessment of efficacy by the investigator Intention to Treat Analysis was done.

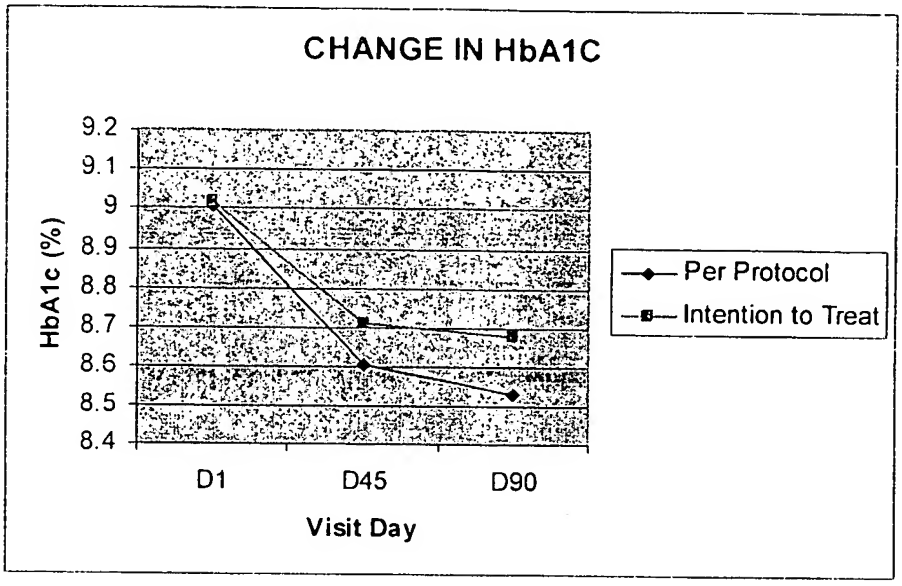
Table: 8 Changes in HbA1c, FBS and PPBS

Efficacy Parameters	Patient Population	Mean ± Std. Dev. (N)						
		Day 1	Day 15	Day 30	Day 45	Day 60	Day 75	Day 90
HbA1c	PP (N = 28)	9.01 ± 0.55	-	-	8.61 ± 1.13[a]	-	-	8.53 ± 2.09[b]
	ITT	9.02 ± 0.54 (38)	-		8.71 ± 1.15[b] (32)	-	-	8.68 ± 2.10[b] (30)
FBS	PP	158.28 ± 26.72 (28)	150.25 ± 33.78 (28)[b]	144.07 ± 32.69 (28)[a]	143.75 ± 33.02 (28)[a]	139.75 ± 34.00 (28)[a]	148.85 ± 35.46 (28)[b]	151.03 ± 47.59 (28)[b]
	ITT	154.18 ± 26.36 (38)	159.02 ± 42.27[b] (38)	145.88 ± 38.81[b] (36)	148.93 ± 36.92[b] (32)	145.23 ± 38.94[b] (30)	148.85 ± 35.46[b] (28)	152.40 ± 46.29[b] (30)
PPBS	PP	216.42 ± 53.66 (35)	214.53 ± 67.02[b] (35)	209.71 ± 53.70[b] (36)	206.85 ± 56.85[b] (32)	186.46 ± 55.45[a] (30)	202.89 ± 60.26[b] (28)	203.82 ± 85.53[b] (30)
	ITT	213.94 ± 55.82 (35)	226.57 ± 79.36[b] (35)	214.33 ± 73.64[b] (36)	212.46 ± 64.18[b] (32)	194.93 ± 63.80[b] (30)	202.89 ± 60.26[b] (28)	209.33 ± 85.16[b] (30)

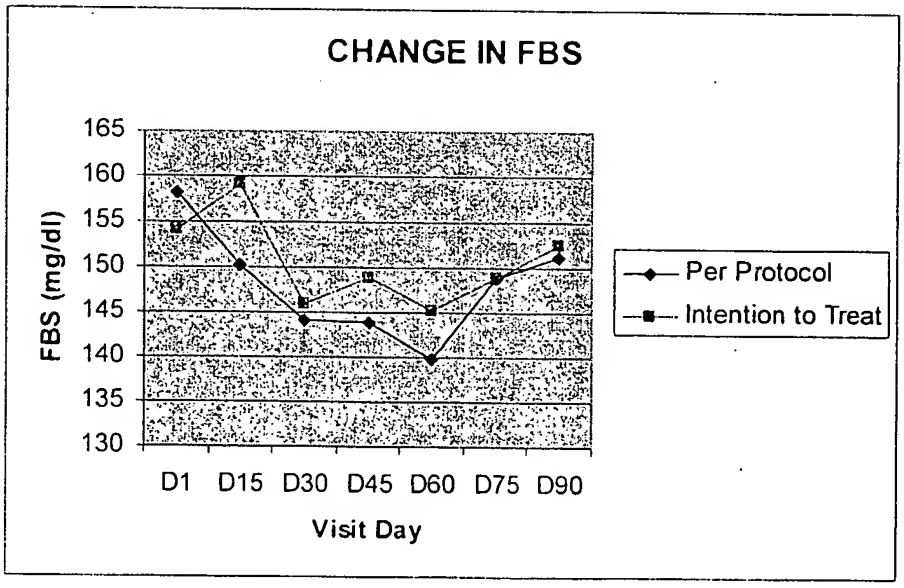
Using Paired t test : a=significant ($p < 0.05$) as compared to baseline

b= not significant ($p > 0.05$) as compared to baseline

Graph 1: Changes in HbA1c



Graph 2: Changes in FBS



Graph 2: Changes in PPBS

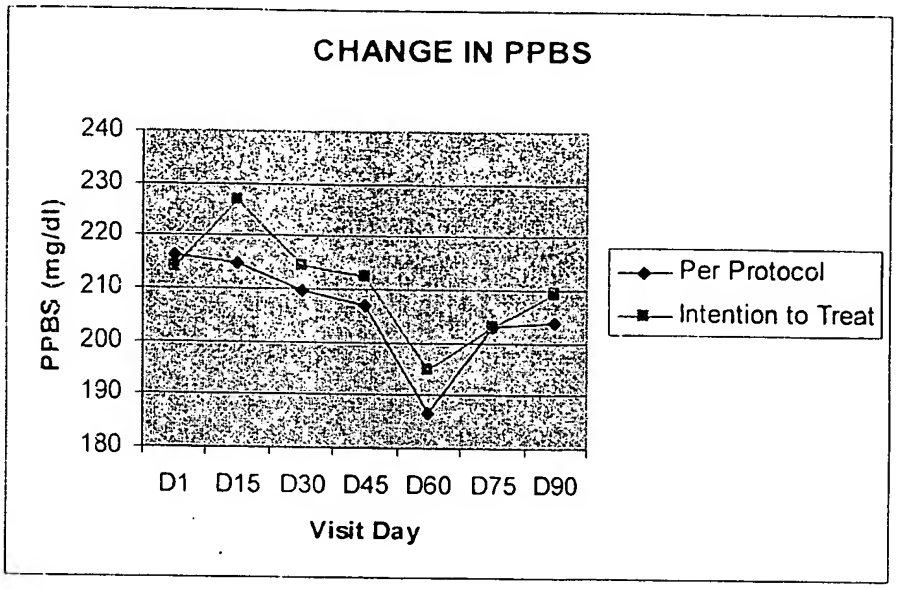


Table 9: Changes in Quality of Life Parameters

Quality of Life Parameters	Patient Population	Mean ± Std. Dev. (N)						
		Day 1	Day 15	Day 30	Day 45	Day 60	Day 75	Day 90
Polyuria	PP (N = 28)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ITT	0.00 (38)	0.00 (38)	0.00 (36)	0.00 (32)	0.00 (30)	0.00 (27)	0.00 (30)
Polyphagia	PP (N = 28)	0.21 ± 0.42	0.21 ± 0.42	0.21 ± 0.42	0.26 ± 0.45	0.21 ± 0.42	0.26 ± 0.45	0.21 ± 0.42
	ITT	0.26 ± 0.45 (38)	0.26 ± 0.45 (38)	0.25 ± 0.44 (36)	0.31 ± 0.47 (32)	0.27 ± 0.45 (30)	0.26 ± 0.45 (27)	0.23 ± 0.43 (30)
Pain	PP (N = 28)	0.25 ± 0.44	0.29 ± 0.46	0.29 ± 0.46	0.33 ± 0.48	0.29 ± 0.46	0.30 ± 0.47	0.29 ± 0.46
	ITT	0.26 ± 0.45 (38)	0.29 ± 0.46 (38)	0.28 ± 0.45 (36)	0.28 ± 0.46 (32)	0.27 ± 0.45 (30)	0.30 ± 0.47 (27)	0.27 ± 0.45 (30)
Weakness	PP (N = 28)	0.18 ± 0.39	0.25 ± 0.44	0.21 ± 0.42	0.26 ± 0.45	0.14 ± 0.36	0.15 ± 0.36	0.14 ± 0.36
	ITT	0.21 ± 0.41 (38)	0.26 ± 0.45 (38)	0.25 ± 0.44 (36)	0.22 ± 0.42 (32)	0.13 ± 0.35 (30)	0.15 ± 0.36 (27)	0.13 ± 0.35 (30)
Leg Cramps	PP (N = 28)	0.11 ± 0.31	0.14 ± 0.36	0.11 ± 0.31	0.00	0.00	0.00	0.00
	ITT	0.13 ± 0.34 (38)	0.16 ± 0.37 (38)	0.14 ± 0.35 (36)	0.00 ± 0.25 (32)	0.00 ± 0.25 (30)	0.00 ± 0.27 (27)	0.10 ± 0.31 (30)

Using Wilcoxon Matched-Pairs Signed-Ranks Test : a=significant ($p < 0.05$) as compared to baseline

b= not significant ($p > 0.05$) as compared to baseline

Using Friedman Two-Way Anova test (Between visits): Non-significant ($p > 0.05$)

Table 10: Assessment of Efficacy by Investigator

Assessment of Efficacy by Investigator	
Grade	**N (%)**
Excellent: Improvement in all parameters	6 (15.80 %)
Good: Improvement in more than 2 parameters	9 (23.70 %)
Average: Improvement in less than 2 parameters	12 (31.60 %)
Poor: No improvement	11 (28.90 %)
Total	**38 (100 %)**

Table 11: Subject's opinion to Continue Treatment

Subject's Opinion about willingness to continue treatment of IP for Type 2 Diabetes Mellitus.	
Grade	**N (%)**
YES	27 (71.10 %)
NO	11 (28.90 %)
Total	**38 (100 %)**

8.3.2 Multi Centre Studies

The table below mentions the distribution of subjects from screening to completion of study visit Day 90 across 2 sites. Due to small sample size, site wise analysis was not done.

The distribution of subjects and the withdrawal/dropouts across all the sites is mentioned in table 11.

Table 12: Site wise Distribution of Subjects

SITEWISE DISPOSITION OF SUBJECTS																
Site	S	R	D1 TO D15		D15 TO D30		D30 TO D45		D45 TO D60		D60 TO D75		D75 TO D90		TOTAL (W/D)	COMPLETED TILL D90
SV01	31	8	W	0	W	0	W	1	W	1	W	0	W	0	W	2	6
			D	0	D	0	D	0	D	0	D	0	D	0	D	0	
SV02	95	31	W	0	W	3	W	3	W	1	W	1	W	0	W	8	22
			D	0	D	0	D	0	D	0	D	1	D	0	D	1	

Number of subjects:

S: Screened

R: Recruited

W: Withdrawn

D: Drop out

8.3.3 Efficacy Results

HbA1c levels decreased but were statistically significant ($p < 0.05$) only at Day 45 when analyzed by per protocol mode group. When analyzed by ITT-mode, there was no change found in HbA1c levels at Day 45 or at Day 90. (Table: 8)

FBS levels decreased but were statistically significant ($p < 0.05$) only at Day 30, Day 45 and Day 60 when compared with baseline when analyzed by per protocol mode. (Table: 8)

When analyzed by ITT mode, FBS levels decreased but were not statistically significant ($p > 0.05$).

PPBS levels decrased but were statistically significant only at Day 60 when analyzed by per protocol mode (Table: 8). When analyzed by ITT mode, PPBS levels decreased but were not statistically significant ($p > 0.05$).

Quality of Life parameters like Polyuria, Polyphagia, Weakness, Pain & Leg Cramps remained unchanged through out the study (Table: 9).

When effcacy was assessed by investigator, it was found that 15.80 %, 23.70, 31.60 and 28.90 % of study patients showed excellent, good, average and poor efficacy respectively (Table: 10).

71.10 % of the study patients showed willingness to continue the study treatment for Type 2 Diabetes Mellitus (Table: 11).

9 DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

This pilot study was designed to evaluate the potential of a combination of Toona sinensis and Heracleum lanatum in maintaining and improving the glycemic state of patients stabilised on OHA who are not well-controlled type 2 diabetes mellitus cases. Hence patients on any stable dose of oral hypoglycemic agent with HBA1c in the range of 8-10 % were selected to participate in the study. The primary objective was to evaluate the efficacy of a combination of Toona sinensis and Heracleum lanatum in patients with type 2 diabetes mellitus. Evaluation of the safety and tolerability of a combination of Toona sinensis and Heracleum lanatum" in terms of tolerability, safety and anti-hyperglycaemic effects were additional trial objectives.

The primary efficacy variable chosen was glycosylated hemoglobin (HbA1c). The profiles of the secondary efficacy variables, Fasting and Post Prandial Plasma Glucose (FPG and PPPG), should be taken into account and be combined with those of HbA1c to enable a complete overall assessment of the efficacy of the investigational product.

HbA1c reduced by 5.33 % at the end of therapy out of which 4.44 % reduction was seen in first 45 days of therapy whereas in the remaining 45 days of therapy was reduction by 0.93 %.

This reduction was found to be statistically significant for the first 45 days of therapy but not at the end of therapy.

Similar profile was seen even with FBS and PPBS levels wherein there was a significant reduction seen in first 60 days therapy after which there was a reduction but was not statistically significant. This may indicate that given the opportunity to continue the medication for longer periods of time, for instance 6 months, there is a chance that HbA1c levels may plateau.

This consistent behaviour of HbA1c, FBS and PPBS concentration patterns induces us to believe that the study provides sufficient evidence of the prospective use of a combination of Toona sinensis and Heracleum lanatum as an anti-diabetic agent.

9.2 Overall Conclusions

A combination of Toona sinensis and Heracleum lanatum when given as an add on therapy along with oral hypoglycemic agent (OHA) to patients with Type 2 Diabetes Mellitus was found to be clinically effective ($p < 0.05$ at Day 45 and Day 60; $p > 0.05$ at Day 90) in providing better glycemic control and it was found to have an excellent safety and tolerability profile under the conditions of the study.

10. REFERENCE LIST

11. APPENDICES

11.1 Study Information

11.1.1 Investigator's Brochure

11.1.2 Protocol and protocol amendments

11.1.3 Sample Case Report Form

11.1.4 Sample Informed Consent Form

11.1.5 List of members and SOP of IEC or IRB

11.1.6 IEC/IRB Approval Letter

11.1.7 Curriculum Vitae Of Study Team Members and Investigators

11.1.8 Investigators Meet Presentation Slides

11.1.9 Site Initiation Reports

11.1.10 Site Monitoring Reports

11.2 Subject Data Listings

11.2.1 Demographic Data

11.2.2 Protocol deviations

11.2.3 Safety Data

11.2.4 Efficacy Data

11.2.5 Adverse event listings

11.2.6 Tables and Graphs not included in report

11.3 Case Report Forms (CRF's) of all Recruited Subjects

11.3.1 CRF's for deaths, other serious adverse events, and withdrawals for adverse events

11.3.2 Other CRF's submitted